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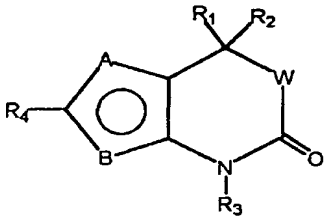
(54) Title: CONTRACEPTIVE COMPOSITIONS CONTAINING CYCLIC CARBAMATES AND AMIDE DERIVATIVES

(57) Abstract

This invention relates to cyclic combination therapies and regimens utilizing, in combination with progestins, estrogens, or both, substituted indoline derivative compounds which are antagonists of the progesterone receptor having general structure (I) wherein A and B are independent substituents selected from S, CH or N; provided that when A is S, B is CH or N; and when B is S, A is CH or N; and A and B cannot both be CH; and when A and B both equal N, one N may be optionally substituted with a C_1 to C_6 alkyl group; R_1 and R_2 are independent substituents selected from the group of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A; or R^1 and R^2 are fused to form optionally substituted 3 to 8 membered spirocyclic alkyl, alkenyl or heterocyclic ring, the heterocyclic ring containing one to three heteroatoms selected from the group of O, S and N; or pharmaceutically useful salts thereof. These methods of treatment may be used for contraception or for the treatment and/or prevention of secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis; polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, or minimization of side effects or cyclic menstrual bleeding. Additional uses of the invention include stimulation of food intake.



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CONTRACEPTIVE COMPOSITIONS CONTAINING CYCLIC CARBAMATES AND AMIDE DERIVATIVES

Field of the Invention

This invention relates to regimens of administering compounds which are antagonists of the progesterone receptor in combination with a progestin, an estrogen, or both.

Background of the Invention

Intracellular receptors (IR) form a class of structurally related genetic regulators known as "ligand dependent transcription factors" (R. M. Evans, *Science*, **240**, 889, 1988). The steroid receptor family is a subset of the IR family, including progesterone receptor (PR), estrogen receptor (ER), androgen receptor (AR), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR).

The natural hormone, or ligand, for the PR is the steroid progesterone, but synthetic compounds, such as medroxyprogesterone acetate or levonorgestrel, have been made which also serve as ligands. Once a ligand is present in the fluid surrounding a cell, it passes through the membrane *via* passive diffusion, and binds to the IR to create a receptor/ligand complex. This complex then translocates to the nucleus of the cell where it binds to a specific gene or genes present in the cell's DNA. Once bound to a specific DNA sequence the complex modulates the production of the mRNA and protein encoded by that gene.

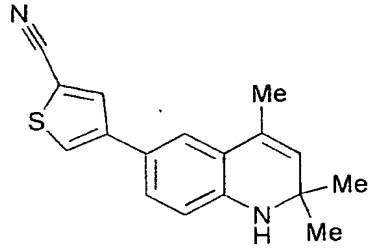
A compound that binds to an IR and mimics the action of the natural hormone is termed an agonist, whilst a compound which inhibits the effect of the hormone is an antagonist. PR agonists (natural and synthetic) are known to play an important role in the health of women. PR agonists are used in birth control formulations, typically in the presence of an ER agonist. ER agonists are used to treat the symptoms of menopause, but have been associated with a proliferative effect on the uterus (in non-hysterectomized women) which can lead to an increased risk of uterine cancers. Co-

administration of a PR agonist reduces/ablates that risk. PR antagonists may also be used in contraception. In this context they may be administered alone (Ulmann, et al, *Ann. N. Y. Acad. Sci.*, **261**, 248, 1995), in combination with a PR agonist (Kekkonen, et al, *Fertility and Sterility*, **60**, 610, 1993) or in combination with a partial ER antagonist such as tamoxifen (WO 96/19997 A1, July 4, 1996).

PR antagonists may also be useful for the treatment of hormone dependent breast cancers (Horwitz, et al, *Horm. Cancer*, 283, pub: Birkhaeuser, Boston, Mass., ed. Vedeckis) as well as uterine and ovarian cancers. PR antagonists may also be useful for the treatment of non-malignant chronic conditions such as fibroids (Murphy, et al, *J. Clin. Endo. Metab.*, **76**, 513, 1993) and endometriosis (Kettel, et al, *Fertility and Sterility*, **56**, 402, 1991).

PR antagonists may also be useful in hormone replacement therapy for post menopausal patients in combination with a partial ER antagonist such as tamoxifen (US 5719136). PR antagonists such as Mifepristone have also been shown to have bone sparing effects in rodents, and as such may be useful in the treatment of osteoporosis associated with the menopause (Barengolts, et al, *Bone*, **17**, 21, 1995). PR antagonists, such as mifepristone and onapristone, have been shown to be effective in a model of hormone dependent prostate cancer, which may indicate their utility in the treatment of this condition in men (Michna, et al, *Ann. N. Y. Acad. Sci.*, ***761***, *224, 1995).*

Jones, *et al,* (U.S. Patent No. 5,688,810) described the PR antagonist dihydroquinoline **1**.



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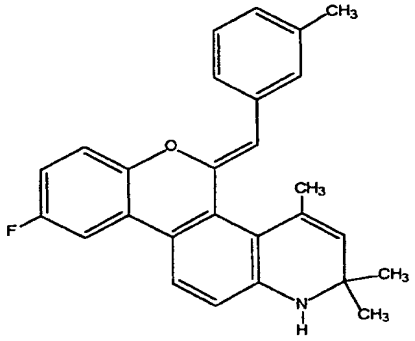
Jones, *et al*, described the enol ether **2** (U.S. Patent No. 5,693,646) as a PR ligand.



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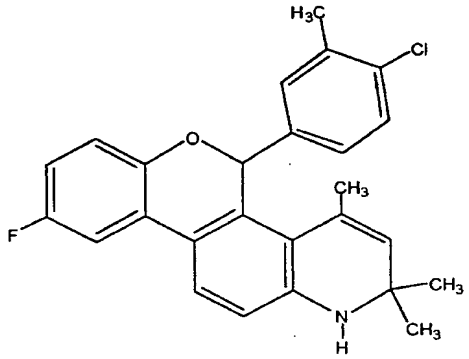
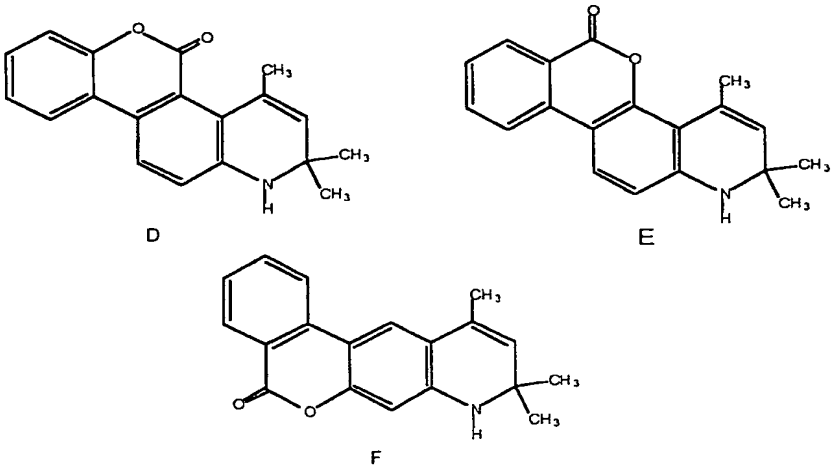
Jones, *et al*, described compound **3** (U.S. Patent No. 5,696,127) as a PR ligand.



3

Zhi, *et al*, described lactones **4**, **5** and **6** as PR antagonists (J. Med. Chem., 41, 291, 1998).



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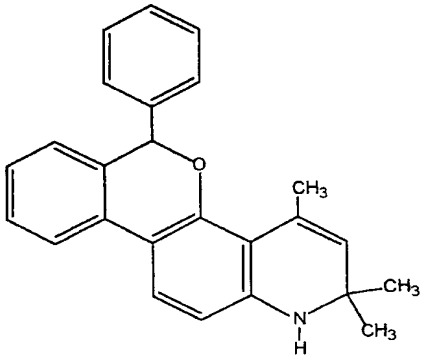
Zhi, *et al*, described the ether 7 as a PR antagonist (J. Med. Chem., **41**, 291, 1998).



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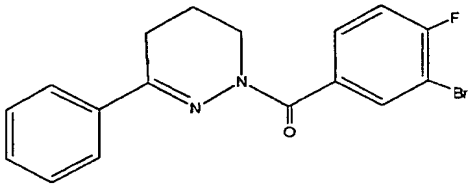
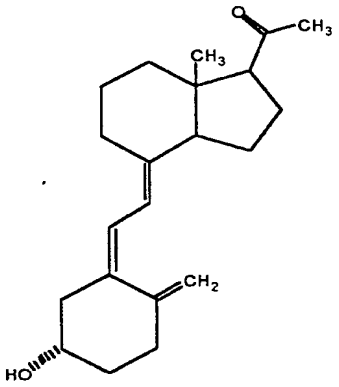
Combs, *et al.*, disclosed the amide **8** as a ligand for the PR (*J. Med. Chem.*, **38**, 4880, 1995).



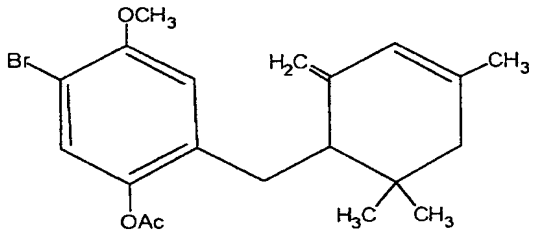
8

Perlman, *et. al.*, described the vitamin D analog **9** as a PR ligand (*Tet. Letters*, **35**, 2295, 1994).



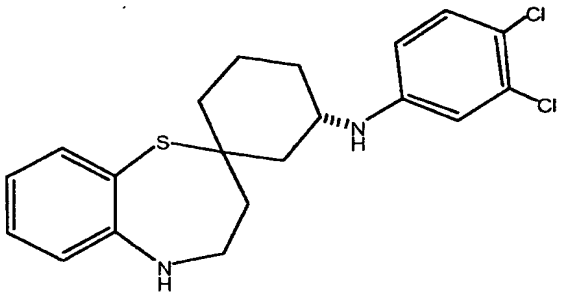
9

Hamann, *et al*, described the PR antagonist **10** (*Ann. N.Y. Acad. Sci.*, **761**, 383, 1995).



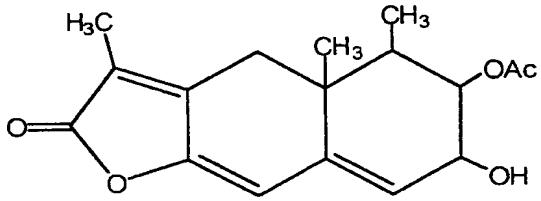
10

Chen, *et al*, described the PR antagonist **11** (Chen, et al, POI-37, 16th Int. Cong. Het. Chem., Montana, 1997).



11

Kurihari, *et. al.*, described the PR ligand **12** (*J. Antibiotics*, **50**, 360, 1997).



12

U.S Patent No. 5,521,166 (Grubb) teaches cyclophasic hormonal regimens comprising an antiprogestin and a progestin wherein the progestin is administered in the alternating presence and absence of an antiprogestin. The disclosed regimens also provide for use of an estrogen for a period of from 2-4 days to prevent breakthrough bleeding.

Description of the Invention.

This invention provides combination therapies and dosing regimens utilizing antiprogestational agents in combination with one or more progestational agents. This invention further provides methods of treatment and dosing regimens further utilizing

in combination with these antiprogestins and progestins, an estrogen, such as ethinyl estradiol.

These regimens and combinations may be administered to a mammal to induce contraception or for the treatment and/or prevention of secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis; polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate. Additional uses of the invention include stimulation of food intake. The uses herein for the treatment and/or prevention of the conditions or diseases described above includes the continuous administration or periodic discontinuation of administration of the invention to allow for minimization of effect dose or minimization of side effects or cyclic menstrual bleeding.

The use of this invention for contraception includes administration, preferably orally, to a female of child bearing age an antiprogestin in combination with an estrogen or progestin or both. These administration regimens are preferably carried out over 28 consecutive days, with a terminal portion of the cycle containing administration of no progestins, estrogens or anti-progestins.

The progestins of these combinations may be administered alone or in combination with an estrogen for the first 14 to 24 days of the cycle, the progestins being administered at a dosage range equal in progestational activity to about 35 μg to about 150 μg levonorgestrel per day, preferably equal in activity to from about 35 μg to about 100 μg levonorgestrel per day. An antiprogestin may then be administered alone or in combination with an estrogen for a period of 1 to 11 days to begin on any cycle day between day 14 and 24. The anti-progestin in these combinations may be administered at a dose of from about 2μg to about 50 μg per day and the estrogen may be administered at a dose of from about 10 μg to about 35 μg per day. In an oral administration, a package or kit containing 28 tablets will include a placebo tablet on those days when the antiprogestin or progestin or estrogen is not administered.

In a preferred embodiment of this invention, the progestins of this invention may be administered alone or in combination with estrogen for the initial 18 to 21 days

of a 28-day cycle, followed by administration of an antiprogestin, alone or in combination with an estrogen, for from 1 to 7 days.

The estrogen to be used in the combinations and formulations of this invention is preferably ethinyl estradiol.

Progestational agents useful with this invention include, but are not limited to, levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethindrone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, drospirenone, nomegestrol, or (17-deacetyl)norgestimate. Among the preferred progestins for use in the combinations of this invention are levonorgestrel, gestodene and trimegestone.

Examples of orally administered regimens of this invention over a 28 day cycle include administration of a progestational agent solely for the first 21 days at a daily dose equal in progestational activity to from about 35 to about 100 μg of levonorgestrel. An antiprogestin compound of this invention may then be administered at a daily dose of from about 2 to 50 mg from day 22 to day 24, followed by no administration or administration of a placebo for days 25 to 28. It is most preferred that the daily dosages of each relevant active ingredient be incorporated into a combined, single daily dosage unit, totaling 28 daily units per 28-day cycle.

In another regimen, a progestational agent may be coadministered for the first 21 days at a daily dose equal in progestational activity to from about 35 to about 150 μg levonorgestrel, preferably equal in activity to from about 35 to about 100 μg levonorgestrel, with an estrogen, such as ethinyl estradiol, at a daily dose range of from about 10 to about 35 μg. This may be followed as described above with an antiprogestin administered at a daily dose of from about 2 to 50 mg from day 22 to day 24, followed by no administration or administration of a placebo for days 25 to 28.

Still another regimen within the scope of this invention will include coadministration from days 1 to 21 of a progestational agent, the progestational agent, preferably levonorgestrel, being administered at a daily dose equal in progestational activity to from about 35 to about 100 μg levonorgestrel, and an estrogen, such as

ethinyl estradiol, at a daily dose range of from about 10 to about 35 μg. This will be followed on days 22 to 24 by coadministration of an antiprogestin (2 to 50 mg/day) and an estrogen, such as ethinyl estradiol, at a daily dose of from about 10 to about 35 μg. From day 25 to day 28, this regimen may be followed by no administration or administration of a placebo.

This invention also kits or packages of pharmaceutical formulations designed for use in the regimens described herein. These kits are preferably designed for daily oral administration over a 28-day cycle, preferably for one oral administration per day, and organized so as to indicate a single oral formulation or combination of oral formulations to be taken on each day of the 28-day cycle. Preferably each kit will include oral tablets to be taken on each the days specified, preferably one oral tablet will contain each of the combined daily dosages indicated.

According to the regimens described above, one 28-day kit may comprise:

a) an initial phase of from 14 to 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel, preferably equal in progestational activity to about 35 to about 100 μg levonorgestrel;

b) a second phase of from 1 to 11 daily dosage units of an antiprogestin compound of this invention, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and

c) optionally, a third phase of an orally and pharmaceutically acceptable placebo for the remaining days of the cycle in which no antiprogestin, progestin or estrogen is administered.

A preferred embodiment of this kit may comprise:

a) an initial phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel, preferably equal in progestational activity to about 35 to about 100 μg levonorgestrel;

b) a second phase of 3 daily dosage units for days 22 to 24 of an antiprogestin compound of this invention, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and

c) optionally, a third phase of 4 daily units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

Another 28-day cycle packaging regimen or kit of this invention comprises:

a) a first phase of from 18 to 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel, preferably equal in activity to from about 35 to about 100 μg levonorgestrel, and, as an estrogen, ethinyl estradiol at a daily dose range of from about 10 to about 35 μg; and

b) a second phase of from 1 to 7 daily dosage units of an antiprogestin of this invention at a daily dose of from about 2 to 50 mg; and

c) optionally, an orally and pharmaceutically acceptable placebo for each of the remaining 0-9 days in the 28-day cycle in which no progestational agent, estrogen or antiprogestin is administered.

A preferred embodiment of the kit described above may comprise:

a) a first phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel, preferably equal in activity to from about 35 to about 100 μg levonorgestrel, and, as an estrogen, ethinyl estradiol at a daily dose range of from about 10 to about 35 μg; and

b) a second phase of 3 daily dosage units for days 22 to 24 of an antiprogestin administered at a daily dose of from about 2 to 50 mg; and

c) optionally, a third phase of 4 daily dose units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

A further 28-day packaged regimen or kit of this invention comprises:

a) a first phase of from 18 to 21 daily dosage units, each containing a progestational agent of this invention at a daily dose equal in progestational activity to about 35 to about 150 μg levonorgestrel, preferably equal in activity to from about 35

to about 100 μg levonorgestrel, and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg;

b) a second phase of from 1 to 7 daily dose units, each daily dose unit containing an antiprogestin of this invention at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 μg; and

c) optionally, an orally and pharmaceutically acceptable placebo for each of the remaining 0-9 days in the 28-day cycle in which no progestational agent, estrogen or antiprogestin is administered.

A preferred embodiment of the package or kit just described comprises:

a) a first phase of 21 daily dosage units, each containing a progestational agent of this invention at a daily dose equal in progestational activity to about 35 to about 150 μg levonorgestrel, preferably from about 35 to about 100 μg levonorgestrel, and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg;

b) a second phase of 3 daily dose units for days 22 to 24, each dose unit containing an antiprogestin of this invention at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 μg; and

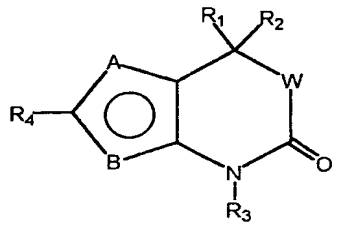
c) optionally, a third phase of 4 daily units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

In each of the regimens and kits just described, it is preferred that the daily dosage of each pharmaceutically active component of the regimen remain fixed in each particular phase in which it is administered. It is also understood that the daily dose units described are to be administered in the order described, with the first phase followed in order by the second and third phases. To help facilitate compliance with each regimen, it is also preferred that the kits contain the placebo described for the final days of the cycle. It is further preferred that each package or kit comprise a pharmaceutically acceptable package having indicators for each day of the 28-day cycle, such as a labeled blister package or dial dispenser packages known in the art.

In this disclosure, the terms anti-progestational agents, anti-progestins and progesterone receptor antagonists are understood to be synonymous. Similarly, progestins, progestational agents and progesterone receptor agonists are understood to refer to compounds of the same activity.

These dosage regimens may be adjusted to provide the optimal therapeutic response. For example, several divided doses of each component may be administered daily or the dose may be proportionally increased or reduced as indicated by the exigencies of the therapeutic situation. In the descriptions herein, reference to a daily dosage unit may also include divided units which are administered over the course of each day of the cycle contemplated.

Compounds of this invention which may be used as the anti-progestational agents in the kits, methods and regimens herein include those of the Formula **I**:



I

wherein:

A and B are independent substituents selected from S, CH or N;

Provided that when A is S, B is CH or N; provided that

when B is S, A is CH or N;

and A and B cannot both be CH;

and when A and B both equal N, one N may be optionally substituted with an C_1 to C_6 alkyl group;

R_1 and R_2 are independent substituents selected from the group of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6

alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

or R^1 and R^2 are fused to form:

a) an optionally substituted 3 to 8 membered spirocyclic alkyl ring, preferably a 3 to 6 membered spirocyclic alkyl ring; or

b) an optionally substituted 3 to 8 membered spirocyclic alkenyl ring, preferably a 3 to 6 membered spirocyclic alkenyl ring; or

c) an optionally substituted 3 to 8 membered spirocyclic ring containing one to three heteroatoms selected from O, S and N, preferably a 3 to 6 membered spirocyclic ring containing one to three heteroatoms;

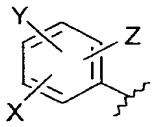
R^A is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^B is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^3 is H, OH, NH_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_1 to C_6 alkenyl, alkynyl, or substituted alkynyl, or COR^C;

R^C is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^4 is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below,



X is selected from halogen, CN, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 thioalkyl, substituted C_1 to C_3 thioalkyl, C_1 to C_3 aminoalkyl, substituted C_1 to C_3

aminoalkyl, NO_2, C_1 to C_3 perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D, $OCOR^D$, or NR^ECOR^D;

R^D is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^E is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

Y and Z are independent independently selected from H, halogen, CN, NO_2, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, or C_1 to C_3 thioalkyl;

or

R^4 is a five or six membered ring with 1, 2, or 3 heteroatoms from the group including O S, SO, SO_2 or NR^5 and containing one or two independent substituents from the group including H, halogen, CN, NO_2 and C_1 to C_3 alkyl, C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, COR^F, or NR^GCOR^F;

R^F is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^G is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^5 is H, or C_1 to C_3 alkyl;

W is O or a chemical bond

or a pharmaceutically acceptable salt thereof.

Among the preferred anti-progestational compounds for use with this invention are those of Formula I wherein:

A and B are independent substituents S, CH or N,

provided that when A is S, B is CH or N; and

when B is S, A is CH or N; and

A and B cannot both be CH; and

when A and B both equal N, one N may be optionally substituted with an C_1 to C_6 alkyl group;

R^1 is H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

R^2 is H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

or R^1 and R^2 are fused to form:

a) an optionally substituted 3 to 8 membered spirocyclic alkyl ring; or

b) an optionally substituted 3 to 8 membered spirocyclic alkenyl ring; or

c) an optionally substituted 3 to 8 membered spirocyclic ring containing one to three heteroatoms selected from the group of O, S and N;

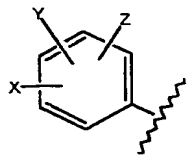
R^A is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^B is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^3 is H, OH, NH_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_1 to C_6 alkenyl, alkynyl, or substituted alkynyl, or COR^C;

R^C is H, C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, aryl, substituted aryl, C_1 to C_4 alkoxy, substituted C_1 to C_4 alkoxy, C_1 to C_4 aminoalkyl, or substituted C_1 to C_4 aminoalkyl;

R^4 is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below:



X is taken from the group including halogen, CN, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 thioalkyl, substituted C_1 to C_3 thioalkyl, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2, C_1 to C_3 perfluoroalkyl, 5-membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D, $OCOR^D$, or NR^ECOR^D;

R^D is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^E is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

Y and Z are independent substituents taken from the group including H, halogen, CN, NO_2, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, or C_1 to C_3 thioalkyl;

or

R^4 is a five or six membered ring with 1, 2, or 3 heteroatoms from the group including O S, SO, SO_2 or NR^5 and containing one or two independent substituents from the group including H, halogen, CN, NO_2 and C_1 to C_3 alkyl, or C_1 to C_3 alkoxy;

R^5 is H or C_1 to C_3 alkyl;

W is O or a chemical bond

or a pharmaceutically acceptable salt thereof.

Further preferred progesterone receptor antagonists are those of Formula I wherein:

A and B are independent substituents from the group including S, CH or N;

provided that when A is S, B is CH or N; and

when B is S, A is CH or N; and

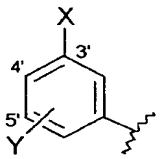
A and B cannot both be CH;

$R^1 = R^2$ and are selected from the group which includes C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, or spirocyclic alkyl constructed by fusing R^1 and R^2 to form a 3 to 6 membered spirocyclic ring;

R^3 is H, OH, NH_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, or COR^C;

R^C is H, C_1 to C_4 alkyl, or C_1 to C_4 alkoxy;

R^4 is a disubstituted benzene ring containing the substituents X and Y as shown below:.

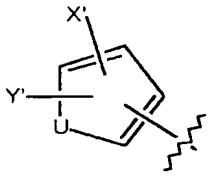


X is selected from the group including halogen, CN, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, NO_2, C_1 to C_3 perfluoroalkyl, 5 membered heterocyclic ring containing 1 to 3 heteroatoms, or C_1 to C_3 thioalkyl;

Y is a substituent on the 4' or 5' position selected from the group of H, halogen, CN, NO_2, C_1 to C_3 alkoxy, C_1 to C_4 alkyl, or C_1 to C_3 thioalkyl;

or

R^4 is a five membered ring with the structure shown below:



U is O, S, or NR^5;

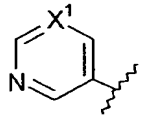
R^5 is H, or C_1 to C_3 alkyl, or C_1 to C_4 CO_2alkyl;

X' is selected from halogen, CN, NO_2, C_1 to C_3 alkyl or C_1 to C_3 alkoxy;

Y' is H or C_1 to C_4 alkyl;

or

R^4 is a six membered ring with the structure:



X^1 is N or CX^2;

X^2 is halogen, CN or NO_2;

W is O or a chemical bond; or a pharmaceutically acceptable salt thereof.

The anti-progestational compounds of this invention may contain an asymmetric carbon atom and some of the compounds of this invention may contain one or more asymmetric centers and may thus give rise to optical isomers and diastereomers. While shown without respect to stereochemistry in Formula I, II, and III, the present invention includes such optical isomers and diastereomers; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof.

The term "alkyl" is used herein to refer to both straight- and branched-chain saturated aliphatic hydrocarbon groups having from one to 8 carbon atoms, preferably from 1 to 6 carbon atoms; "alkenyl" is intended to include both straight- and branched-chain alkyl group having from 2 to 8 carbon atoms, preferably 2 to 6 carbon atoms, with at least one carbon-carbon double bond; "alkynyl" group is intended to cover both straight- and branched-chain alkyl group having from 2 to 8 carbon atoms, preferably 2 to 6 carbon atoms, with at least one carbon-carbon triple bond.

The terms "substituted alkyl", "substituted alkenyl", and "substituted alkynyl" refer to alkyl, alkenyl, and alkynyl as just described having one or more substituents from the group including halogen, CN, OH, NO_2, amino, aryl, heterocyclic, substituted aryl, substituted heterocyclic, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, arylthio. These substituents may be attached to any carbon

of alkyl, alkenyl, or alkynyl group provided that the attachment constitutes a stable chemical moiety.

The term "aryl" is used herein to refer to an aromatic system which may be a single ring or multiple aromatic rings fused or linked together as such that at least one part of the fused or linked rings forms the conjugated aromatic system. The aryl groups include but not limited to phenyl, naphthyl, biphenyl, anthryl, tetrohydronaphthyl, phenanthryl.

The term "substituted aryl" refers to aryl as just defined having one or more substituents from the group including halogen, CN, OH, NO_2, amino, alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio.

The term "heterocyclic" is used herein to describe a stable 4- to 7-membered monocyclic or a stable multicyclic heterocyclic ring which is saturated, partially unsaturated, or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group including N, O, and S atoms. The N and S atoms may be oxidized. The heterocyclic ring also includes any multicyclic ring in which any of above defined heterocyclic rings is fused to an aryl ring. The heterocyclic ring may be attached at any heteroatom or carbon atom provided the resultant structure is chemically stable. Such heterocyclic groups include, for example, tetrahydrofuran, piperidinyl, piperazinyl, 2-oxopiperidinyl, azepinyl, pyrrolidinyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, morpholinyl, indolyl, quinolinyl, thienyl, furyl, benzofuranyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and isoquinolinyl.

The term "substituted heterocyclic" is used herein to describe the heterocyclic just defined having one or more substituents selected from the group which includes halogen, CN, OH, NO_2, amino, alkyl, substituted alkyl, cycloalkyl, alkenyl, substituted alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio. The term "alkoxy" is used herein to refer to the OR group, where R is alkyl or substituted alkyl. The term "aryloxy" is used herein to refer to the

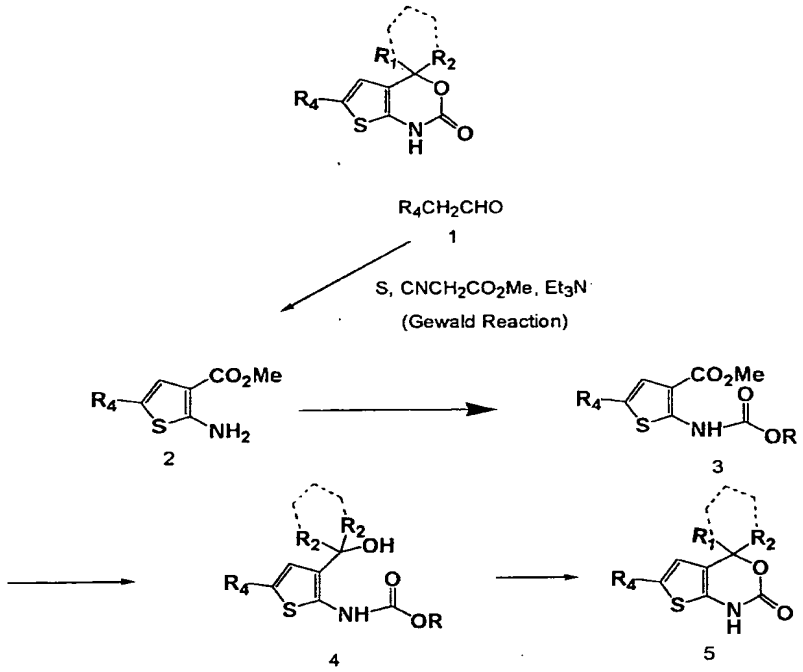
OR group, where R is aryl or substituted aryl. The term "alkylcarbonyl" is used herein to refer to the RCO group, where R is alkyl or substituted alkyl. The term "alkylcarboxy" is used herein to refer to the COOR group, where R is alkyl or substituted alkyl. The term "aminoalkyl" refers to both secondary and tertiary amines wherein the alkyl or substituted alkyl groups may be either same or different and the point of attachment is on the nitrogen atom. The term "thioalkyl" is used herein to refer to the SR group, where R is alkyl or substituted alkyl. The term "halogen" refers to Cl, Br, F, and I element.

The anti-progestin compounds of this invention can be prepared following the Schemes illustrated below:

CYCLOCARBAMATE DERIVATIVES

Processes for preparing thiophene cyclocarbamate derivatives

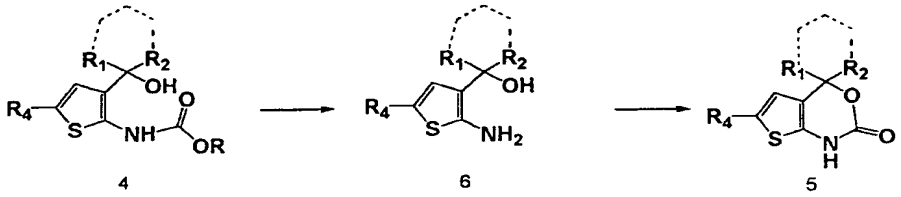
A. Methods for synthesizing the thiophene cyclocarbamate compounds depicted in Scheme 1 are described below:



Scheme 1

Thus the amino thiophene ester **2** was prepared according to a literature procedure involving the Gewald reaction (see Comprehensive Heterocyclic Chemistry II. A Review of the Literature 1982-1995. A.R. Katritsky et al. Vol. 2 page 639), i.e. the reaction of a suitably substituted aromatic acetaldehyde with sulfur and methyl cyanoacetate in refluxing methanol (Scheme 1). Reaction of the 2-amino group with a suitable chloroformate or carbonate affords the protected amine **3**. This can be accomplished by allowing **2** to react with a chloroformate or carbonate derivative such as methyl chloroformate, ethyl chloroformate, allyl chloroformate, 2-(trimethylsilyl)ethyl chloroformate or di-tert-butyldicarbonate in a solvent such as benzene, toluene, xylene, dichloromethane, tetrahydrofuran or pyridine. The reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0°C up to the reflux temperature of the solvent and may require the presence of a base such as 4-

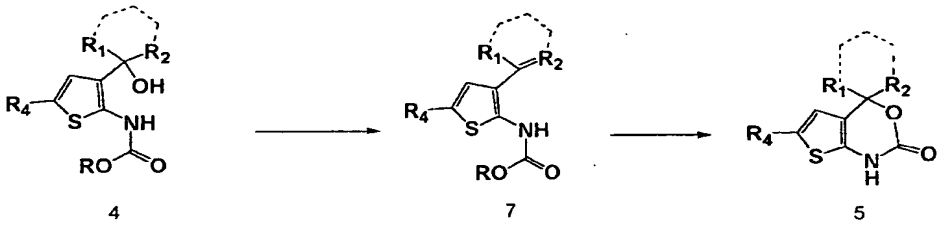
dimethylaminopyridine, triethylamine, pyridine or di-isopropyl ethylamine. Treatment of the protected amino compound **3** with an organo-metallic reagent such as a Grignard reagent, an alkyl or aryl-zinc reagent, an alkyl or aryl lithium reagent in an inert solvent (tetrahydrofuran, diethylether) under an inert atmosphere (nitrogen or argon) at a suitable temperature from 0°C up to reflux temperature of the solvent will then provide the tertiary alcohol **4**. Compound **4** may then be subjected to basic conditions to effect ring closure to give the cyclocarbamate derivative **5**. Suitable conditions would involve treatment of 4 with a base such as potassium hydroxide in a solvent such as ethanol or potassium t-butoxide in a solvent such as tetrahydrofuran. The reaction can be carried out in an inert atmosphere (nitrogen or argon) from 0°C up to the reflux temperature of the solvent.



4 6 5

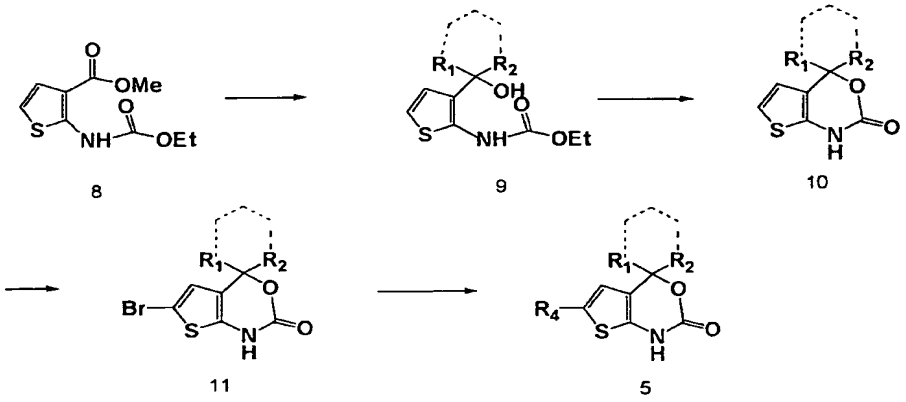
Scheme 2

Alternatively the carbamate protecting group present in **4** may be removed under conditions appropriate for its removal to afford **6** (Scheme 2). Subsequent ring closure of **6** with a reagent such as phosgene, carbonyldiimidazole or dimethyl carbonate in an appropriate solvent (tetrahydrofuran, dichloromethane, benzene, etc.) also will provide access to **5**.



Scheme 3

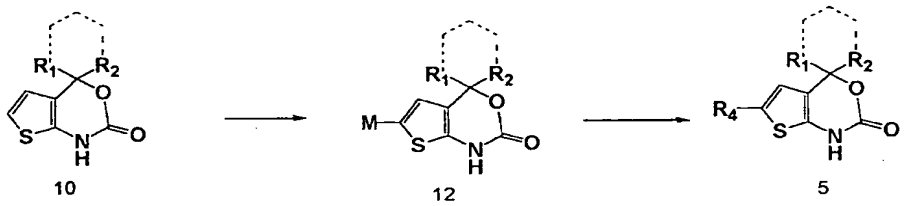
Alternatively, compound **4** may be dehydrated to afford the isopropene derivative **7** (Scheme 3). Suitable conditions for the dehydration would be the use of a reagent such as acetic anhydride, methanesulfonyl chloride, p-toluenesulfonyl chloride or trifluoromethane sulfonyl chloride or anhydride, in a solvent such as pyridine, tetrahydrofuran, dichloromethane or benzene. The reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0°C up to the reflux temperature of the solvent and may require the presence of a base such as 4-dimethylaminopyridine, triethylamine, pyridine or di-isopropyl ethylamine. Exposure of **7** to acidic conditions would then afford ring closure to give **5**. Suitable conditions would be the use of an acid such as p-toluenesulfonic acid, methanesulfonic acid or camphorsulfonic acid in a solvent such as dichloromethane, benzene, toluene or tetrahydrofuran. The reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0°C up to the reflux temperature of the solvent.



Scheme 4

An alternative route to **5** is shown in Scheme **4**. Treatment of the previously described compound **8** (M. Sugiyama, T. Sakamoto, K. Tabata, K. Endo, K. Ito, M. Kobayashi, H. Fukiumi, Chem. Pharm. Bull., **37**(8): 2091 (1989)) with an organometallic reagent such as a Grignard reagent, an alkyl or aryl zinc reagent, an alkyl or aryl lithium reagent in an inert solvent (tetrahydrofuran, diethylether) under an inert atmosphere (nitrogen or argon) at a suitable temperature from 0° C up to reflux temperature of the solvent will then provide the tertiary alcohol **9**. Compound **9** may then be subjected to basic conditions to effect ring closure to give the cyclocarbamate derivative **10**. Suitable conditions would involve treatment of **10** with a base such as potassium hydroxide in a solvent such as ethanol or potassium t-butoxide in a solvent such as tetrahydrofuran. The reaction can be carried out in an inert atmosphere (nitrogen or argon) from 0° C up to the reflux temperature of the solvent. Compound **10** may then be converted to the brominated derivative **11**. Suitable conditions would be treatment with bromine or N-bromosuccinimide in a solvent such as dichloromethane, tetrahydrofuran or acetic acid. The reaction can be carried out in an inert atmosphere (nitrogen or argon) from 0° C up to the reflux temperature of the solvent in the presence of an additive such as silica gel. Subsequent reaction of **11** with an aryl or heteroaryl boronic acid, boronic acid anhydride or trialkyl stannane then

provides access to the desired biaryl compound **5**. The reaction can be carried out in a solvent such as acetone, ethanol, benzene, toluene or tetrahydrofuran, under an inert atmosphere (nitrogen or argon) from 0° C up to the reflux temperature of the solvent, in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium (0) or palladium acetate and may require an additive such as sodium carbonate, cesium fluoride or potassium phosphate.

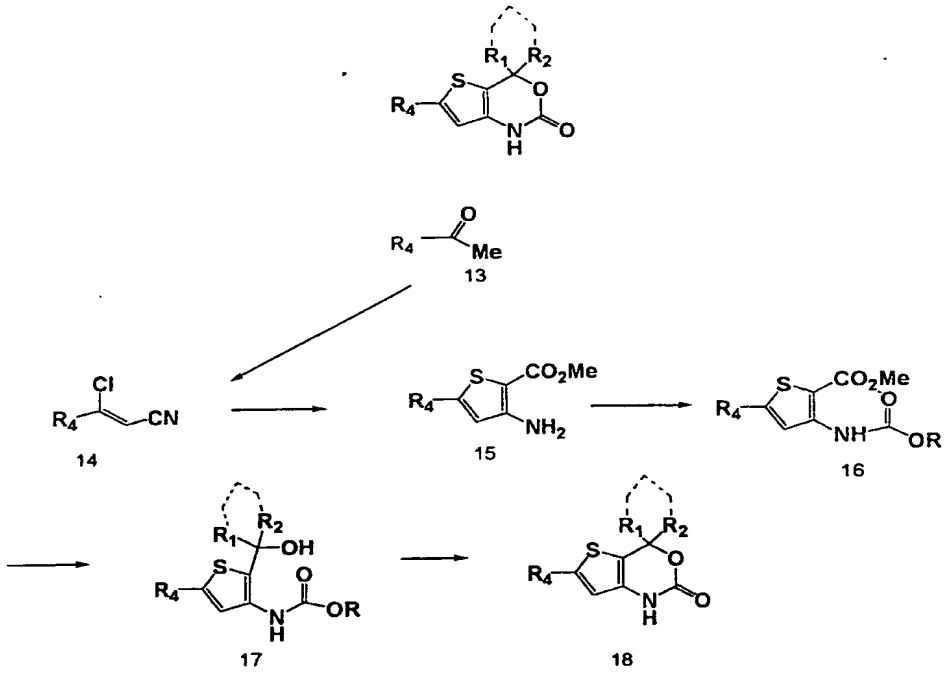


10 12 5

Scheme 5

Alternatively, **10** (Scheme 5) may be treated at low temperature with a reagent such as an alkyl lithium or lithium amide in an inert solvent such as tetrahydrofuran, and then converted to a boronic acid **12** (M= $B(OH)_2$) under the action of trimethyl or triisopropyl borate, or into a stannane via reaction with trimethyltin chloride or bis(trimethyltin). Subsequent reaction of **12** with an aryl or heteroaryl bromide or iodide in the presence of a palladium catalyst such as tetrakis(triphenylphosphine) palladium (0) or palladium acetate and may require an additive such as sodium carbonate, cesium fluoride or potassium phosphate, would then effect conversion into the desired thiophene cyclocarbamate **5**.

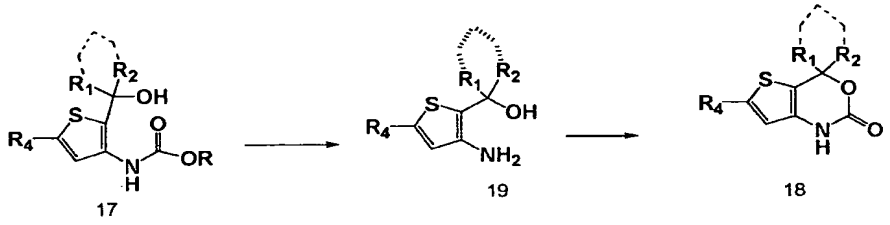
B. Methods for synthesizing the thiophene cyclocarbamate compounds depicted in Scheme 6 are described below:



Scheme 6

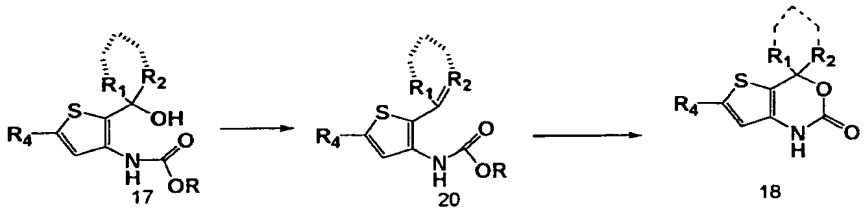
The amino thiophene compounds **15** (Scheme 6) are prepared according to a literature procedure (Comprehensive Heterocyclic Chemistry II. A Review of the Literature 1982-1995. A.R. Katrisky et al., Vol. 2, page 639) which involves treating a suitably substituted aromatic methyl ketone **13** with phosphorus oxychloride in N,N-dimethyl formamide to afford the chloro cyano olefin derivative **14.** Allowing **14** to react with methyl mercaptoacetate in methanol containing sodium methoxide affords the key aminothiophene carboxylate starting material. Reaction of the 2-amino group with a suitable chloroformate or carbonate affords the protected amine **16**. This can be accomplished by allowing **15** to react with a chloroformate or carbonate derivative such as methyl chloroformate, ethyl chloroformate, allyl chloroformate, 2-(trimethylsilyl)ethyl chloroformate or di-tert-butyldicarbonate in a solvent such as

benzene, toluene, xylene, dichloromethane, tetrahydrofuran or pyridine. The reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0° C up to the reflux temperature of the solvent and may require the presence of a base such as 4-dimethylaminopyridine, triethylamine, pyridine or di-isopropyl ethylamine. Treatment of the protected amino compound **16** with an organo-metallic reagent such as a Grignard reagent, an alkyl or aryl-zinc reagent, an alkyl or aryl lithium reagent in an inert solvent (tetrahydrofuran, diethylether) under an inert atmosphere (nitrogen or argon) at a suitable temperature from 0° C up to reflux temperature of the solvent will then provide the tertiary alcohol **17**. Compound **17** may then be subjected to basic conditions to effect ring closure to give the cyclocarbamate derivative **18**. Suitable conditions would involve treatment of **4** with a base such as potassium hydroxide in a solvent such as ethanol or potassium t-butoxide in tetrahydrofuran. The reaction can be carried out in an inert atmosphere (nitrogen or argon) from 0° C up to the reflux temperature of the solvent.



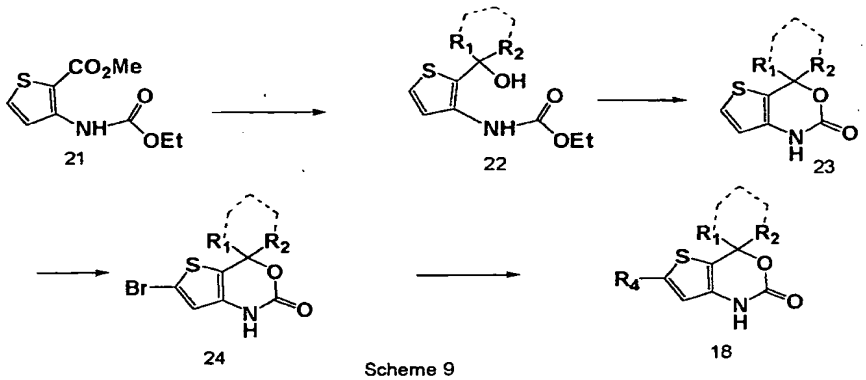
Scheme 7

Alternatively the carbamate protecting group present in **17** may be removed under conditions appropriate for its removal to afford **19** (Scheme 7). Subsequent ring closure of **19** with a reagent such as phosgene, carbonyldiimidazole or dimethyl carbonate in an appropriate solvent (tetrahydrofuran, dichloromethane, benzene, etc.) also will provide access to **18**.



Scheme 8

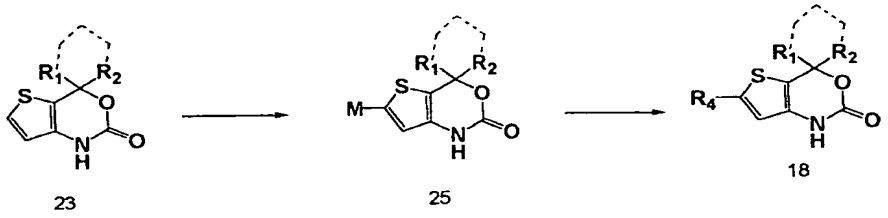
Alternatively, compound **17** may be dehydrated to afford the isopropene derivative **20** (Scheme 8). Suitable conditions for the dehydration would be the use of a reagent such as acetic anhydride, methanesulfonyl chloride, p-toluenesulfonyl chloride or trifluoromethane sulfonyl chloride or anhydride, in a solvent such as pyridine, tetrahydrofuran, dichloromethane or benzene. The reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0°C up to the reflux temperature of the solvent and may require the presence of a base such as 4-dimethylaminopyridine, triethylamine, pyridine or di-isopropyl ethylamine. Exposure of **20** to acidic conditions would then afford ring closure to give **18**. Suitable conditions would be the use of an acid such as p-toluenesulfonic acid, methanesulfonic acid or camphorsulfonic acid in a solvent such as dichloromethane, benzene, toluene or tetrahydrofuran. The reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0°C up to the reflux temperature of the solvent.



Scheme 9

An alternative route to **18** is shown in Scheme 9. Treatment of the previously described compound **21**, as taught by H. Fukiumi, M. Sugiyama, T. Sakamoto, Chem Pharm Bull., 37(5):1197 (1989), with an organo-metallic reagent such as a Grignard reagent, an alkyl or aryl zinc reagent, an alkyl or aryl lithium reagent in an inert solvent (tetrahydrofuran, diethylether) under an inert atmosphere (nitrogen or argon) at a suitable temperature from 0° C up to reflux temperature of the solvent will then provide the tertiary alcohol **22**. Compound **22** may then be subjected to basic conditions to effect ring closure to give the cyclocarbamate derivative **23**. Suitable conditions would involve treatment of **22** with a base such as potassium hydroxide in a solvent such as ethanol or potassium t-butoxide in tetrahydrofuran. The reaction can be carried out in an inert atmosphere (nitrogen or argon) from 0° C up to the reflux temperature of the solvent. Compound **23** may then be converted to the brominated derivative **24**. Suitable conditions would be treatment with bromine or N-bromosuccinimide in a solvent such as dichloromethane, tetrahydrofuran or acetic acid. The reaction can be carried out in an inert atmosphere (nitrogen or argon) from 0° C up to the reflux temperature of the solvent in the presence of an additive such as silica gel. Subsequent reaction of **24** with an aryl or heteroaryl boronic acid boronic acid anhydride or trialkyl stannane then provides access to the desired biaryl compound **18**. The reaction can be carried out in a solvent such as acetone, ethanol, benzene, toluene

or tetrahydrofuran, under an inert atmosphere (nitrogen or argon) from 0° C up to the reflux temperature of the solvent, in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium (0) or palladium acetate and may require an additive such as sodium carbonate, cesium fluoride or potassium phosphate.

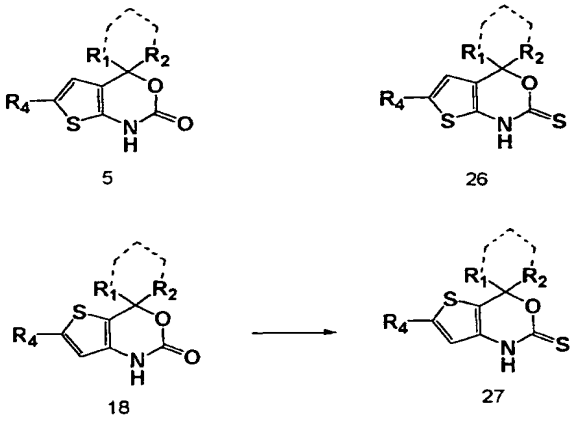


23 25 18

Scheme 10

Alternatively, **23** (Scheme 10) may be treated at low temperature with a reagent such as an alkyl lithium or lithium amide in an inert solvent such as tetrahydrofuran, and then converted to a boronic acid **25** (M= $B(OH)_2$) under the action of trimethyl or triisopropyl borate, or into a stannane via reaction with trimethyltin chloride or bis(trimethyltin). Subsequent reaction of **25** with an aryl or heteroaryl bromide or iodide in the presence of a palladium catalyst such as tetrakis(triphenylphosphine) palladium (0) or palladium acetate and may require an additive such as sodium carbonate, cesium fluoride or potassium phosphate, would then effect conversion into the desired thiophene cyclocarbamate **18**.

C. Method for synthesizing the thiophene thiocyclocarbamate compounds **26** and **27** depicted in Scheme 11 are described below:

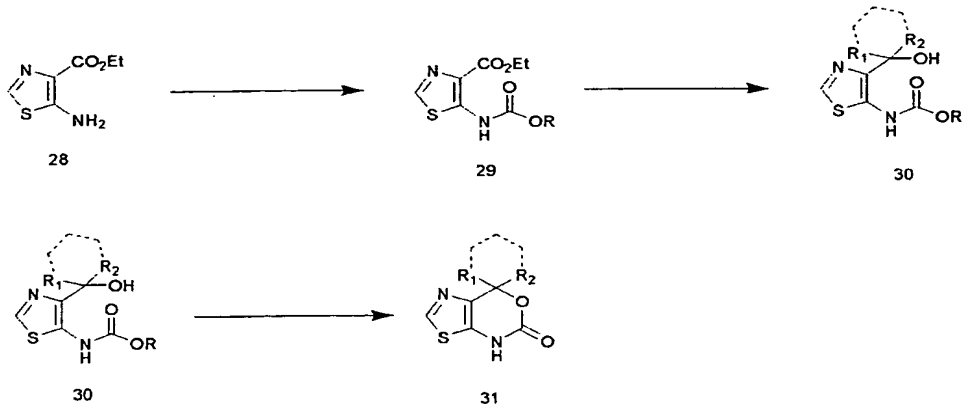


Scheme 11

Thiophene thiocyclocarbamates **26** and **27** may be obtained directly by treating **5** and **18** respectively with phosphorus pentasulfide in refluxing pyridine. Alternatively **5** and **18** may be treated with Lawesson's reagent ([2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide]) in refluxing pyridine to afford **26** and **27**, respectively.

Process for making thiazole cyclocarbamate derivatives.

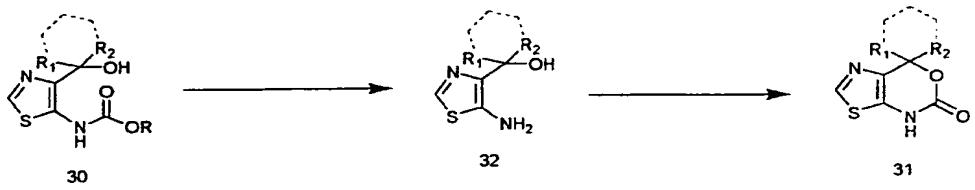
Methods for preparing the thiazole cyclocarbamate compounds are described below.



Scheme 12

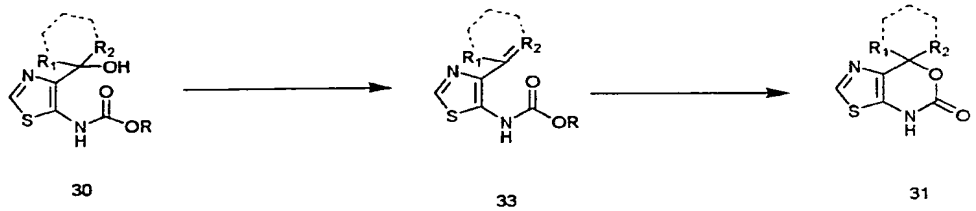
Thus the thiazole **28** was prepared according to a literature procedure, scheme12 by B. Golankiewicz and P. Januszczyk, *Tetrahedron*, **41**:5989 (1985). Reaction of the amine **28** with a suitable chloroformate or carbonate then gives the protected amine **29**. This may be accomplished by reacting compound **28** with a chloroformate or carbonate derivative such as methylchloroformate, ethylchloroformate, allylchloroformate, 2-(trimethylsilyl)ethylchloroformate or di-tert-butyldicarbonate in a solvent such as dichloromethane, THF, benzene, xylene or pyridine. The reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0 °C up to the reflux temperature of the solvent and may require the presence of a base such as 4-dimethylaminopyridine, triethylamine, pyridine or di-isopropyl ethylamine. Exposure of compound **29** to an organo-metallic reagent such as a Grignard reagent, an alkyl or aryl-zinc reagent, an alkyl or aryl lithium reagent in an inert solvent (THF, diethyl ether) under an inert atmosphere (nitrogen or argon) at a suitable temperature from 0 °C up to the reflux temperature of the solvent will then provide the alcohol **30**. Compound **30** may then be exposed to basic conditions to effect ring closure to give the cyclocarbamate derivative **31**. Suitable conditions would involve treatment of compound **30** with a base such as potassium hydroxide in a

solvent such as ethanol. The reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0 °C up to the reflux temperature of the solvent.



Scheme 13

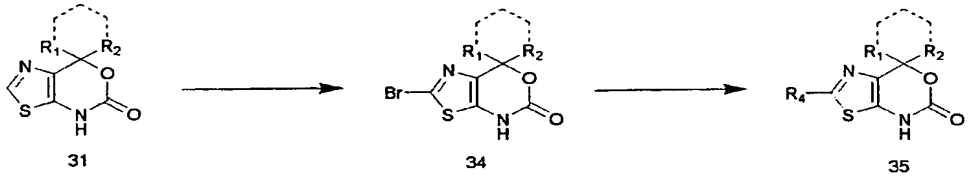
Alternatively the carbamate protecting group present in compound **30** may be removed under conditions appropriate for its removal to afford compound **32** as taught by T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, second ed., Wiley-Interscience (1991). Subsequent ring closure of compound **32** with a reagent such as phosgene, carbonyl diimidazole or dimethyl carbonate in an appropriate solvent (THF, dichloromethane, benzene, etc) will also provide access to compound **31**.



Scheme 14

Alternatively, if compound **30** is a tertiary alcohol then it may be dehydrated to afford the isopropene derivative **33**, scheme 3. Suitable conditions for the dehydration would the use of a reagent such as acetic anhydride, methanesulfonyl chloride, p-

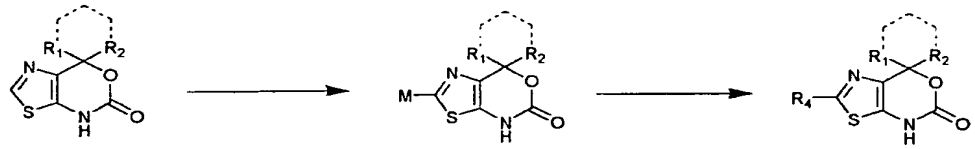
toluenesulfonyl chloride or trifluoromethane sulfonyl chloride or anhydride, in a solvent such as pyridine, THF, dichloromethane or benzene. The reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0 °C up to the reflux temperature of the solvent and may require the presence of a base such as 4-dimethylaminopyridine, triethylamine, pyridine or di-isopropyl ethylamine. Exposure of compound **33** to acidic conditions would then afford ring closure to give compound **31**. Suitable conditions would be the use of an acid such as p-toluenesulfonic acid, methanesulfonic acid or camphorsulfonic acid in a solvent such as dichloromethane, benzene, toluene or THF and the reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0 °C up to the reflux temperature of the solvent.



Scheme 15

Compound **31** may then be converted into the bromide **34**, scheme 15. Suitable conditions would be exposure to bromine or N-bromosuccinimide in a solvent such as dichloromethane, THF or acetic acid, the reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0 °C up to the reflux temperature of the solvent in the presence of an additive such as silica gel. Subsequent reaction of compound **34** with an aryl or heteroaryl boronic acid, boronic acid anhydride or trialkyl stannane then provides access to the desired biaryl compound **35**. The reaction can be carried out in a solvent such as acetone, ethanol, benzene, toluene or THF, under an inert atmosphere (nitrogen or argon) from 0 °C up to the reflux temperature of the solvent, in the presence of a palladium catalyst such as tetrakis(triphenylphosphine) palladium

(0) or palladium acetate and may require an additive such as sodium carbonate, cesium fluoride or potassium phosphate.



31 36 35

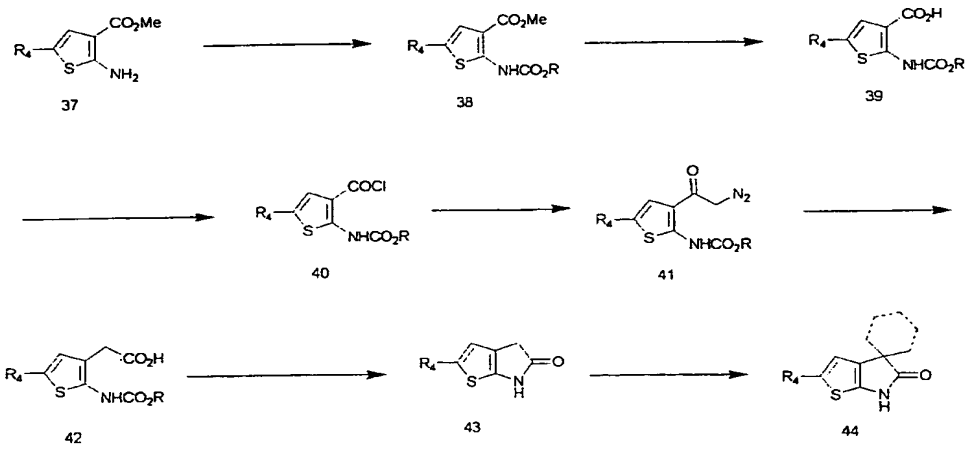
Scheme 16

Alternatively compound **31** may be treated at low temperature with a reagent such as an alkyl lithium or lithium amide in an inert solvent such as THF, and then converted into a boronic acid (M = $B(OH)_2$) **36** under the action of trimethyl or triisopropyl borate, or into a stannane under the action of trimethyltin chloride or bis(trimethyltin), Scheme 16. Subsequent reaction with an aryl or heteroaryl bromide or iodide in the presence of a palladium catalyst such as tetrakis(triphenylphosphine) palladium (0) or palladium acetate and may require an additive such as sodium carbonate, cesium fluoride or potassium phosphate would then effect conversion into the desired compound **35**.

AMIDE DERIVATIVES

Process for making amide thiophene derivatives.

A method for preparing thiophene derivatives is described below, scheme 17.



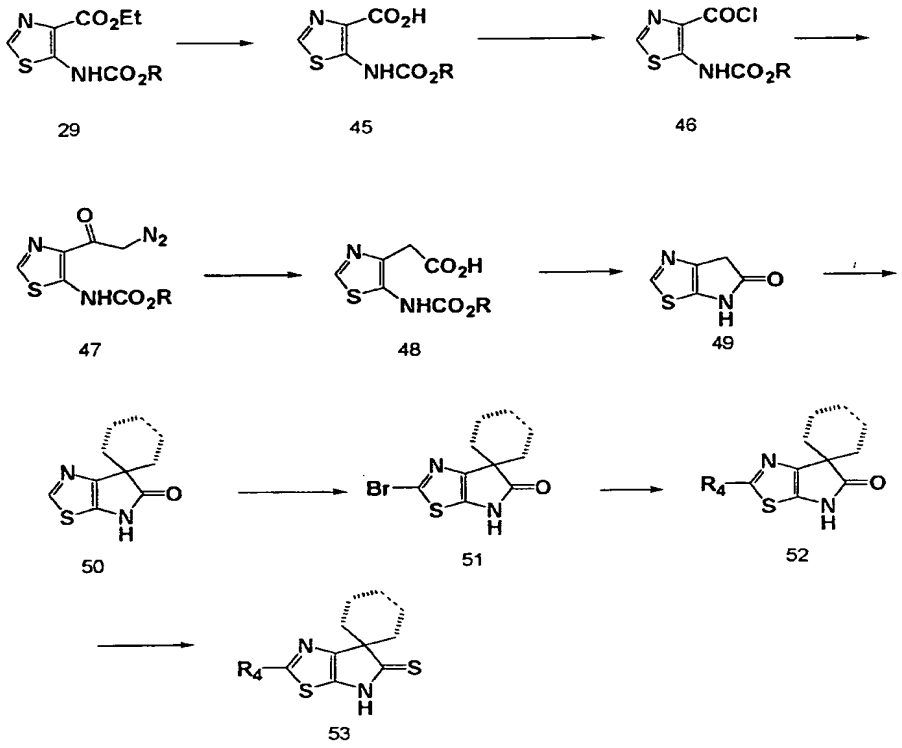
Scheme 17

Thus the amine **37** is converted into a carbamate, such as a *tert*-butyl carbamate as described in scheme 1 for the preparation of compound 2. Hydrolysis of the ester **38** under basic conditions, for example lithium or sodium hydroxide in THF or methanol at room temperature then gives the acid **39**. Conversion of the acid **39** into the acid chloride **40** is accomplished under standard conditions, thionyl chloride or oxalyl chloride either neat or in the presence of a solvent such as dichloromethane and an additive such as a catalytic amount of N,N-dimethylformamide. Compound **40** is then reacted with diazomethane or trimethylsilyldiazomethane in an inert solvent such as THF or dichloromethane, and the product diazoketone **41** is then rearranged in the presence of silver (I) oxide to afford the acid **42**. Treatment of compound **42** under conditions that specifically remove the protecting carbamate functionality, for example acidic conditions, will then affect cyclization to give compound **43**. Reaction of compound **43** with an alkylating agent such as an alkyl iodide, bromide, tosylate or mesylate, or a bis-alkyl iodide, bromide, tosylate or mesylate, under basic conditions, for example butyl lithium in the presence of N,N,N,N-tetramethylene diamine in a solvent such as THF under an inert atmosphere (nitrogen or argon) at a temperature

between -78 °C and the boiling point of the solvent, will then afford the alkylated derivative **44**.

Process for making thiazole derivatives.

A method for preparing thiazole derivatives is described below, scheme 18.



Scheme 18

Hydrolysis of the ester **29** under basic conditions, for example lithium or sodium hydroxide in THF or methanol at room temperature then gives the acid **45**. Conversion of the acid **45** into the acid chloride **46** is accomplished under standard

conditions, for example thionyl chloride or oxalyl chloride either neat or in the presence of a solvent such as dichloromethane and an additive such as a catalytic amount of N,N-dimethylformamide. Compound **46** is then reacted with diazomethane or trimethylsilyldiazomethane in an inert solvent such as THF or dichloromethane, and the product diazoketone **47** is then rearranged in the presence of silver (I) oxide to afford the acid **48**. Treatment of compound **48** under conditions that specifically remove the protecting carbamate functionality, for example acidic conditions, will then affect cyclization to give the heterocycle **49**. Reaction of compound **49** with an alkylating agent such as an alkyl iodide, bromide, tosylate or mesylate, or a bis-alkyl iodide, bromide, tosylate or mesylate, under basic conditions, for example butyl lithium in the presence of N,N,N,N-tetramethylene diamine in a solvent such as THF under an inert atmosphere (nitrogen or argon) at a temperature between -78 °C and the boiling point of the solvent, will then afford the alkylated heterocycle **50**. Compound **50** may then be converted into the bromide **51**. Suitable conditions would be exposure to bromine or N-bromosuccinimide in a solvent such as dichloromethane, THF or acetic acid, the reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0 °C up to the reflux temperature of the solvent in the presence of an additive such as silica gel. Subsequent reaction of compound **51** with an aryl or heteroaryl boronic acid, boronic acid anhydride or trialkyl stannane then provides access to the desired biaryl compound **52**. The reaction can be carried out in a solvent such as acetone, ethanol, benzene, toluene or THF, under an inert atmosphere (nitrogen or argon) from 0 °C up to the reflux temperature of the solvent, in the presence of a palladium catalyst such as tetrakis(triphenylphosphine) palladium (0) or palladium acetate and may require an additive such as sodium carbonate, cesium fluoride or potassium phosphate. The thione derivative, compound **53**, may be obtained directly by treating **52** with phosphorus pentasulfide in refluxing pyridine. Alternatively **52** may be treated with Lawesson's reagent in refluxing pyridine to afford **53**.

The anti-progestin compounds of the formulations of the present invention can be used in the form of salts derived from pharmaceutically or physiologically

acceptable acids or bases. These salts include, but are not limited to, the following salts with inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid and, as the case may be, such organic acids as acetic acid, oxalic acid, succinic acid, and maleic acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium in the form of esters, carbamates and other conventional "pro-drug" forms, which, when administered in such form, convert to the active moiety *in vivo*.

These methods of treatment may be used for contraception or for the treatment and/or prevention of secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis; polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, or minimization of side effects or cyclic menstrual bleeding. Additional uses of the invention include stimulation of food intake.

When the combined compounds are employed for the utilities described above, they may be combined with one or more pharmaceutically acceptable carriers or excipients, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 25 to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

These active compounds may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the

particular form of administration desired. Adjuvents customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid, polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringe ability exits. It must be stable under conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacterial and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oil.

The following non-limiting examples are illustrative of exemplary compound **5.**

EXAMPLE 1

6-(3-chlorophenyl)-1,4-dihydro-4,4-dimethyl-2H-thieno[2,3-d][1,3]oxazine-2-one

2-(3-Chlorobenzyl)acetaldehyde

To a 25°C solution of 3-chlorostyrene in anhydrous CH_2Cl_2 (10.0g, 72.15 mmol) was added a well-stirred solution of $Pb(OAc)_4$ (35.2g, 79.4mmol) in trifluoroacetic acid (150mL), dropwise. Reaction was completed within 30 minutes of the addition and after being stirred for a further 30 minutes, the mixture was poured into water, extracted with ether (3X), the combined organic layers were washed with saturated $NaHCO_3$ solution, water, dried ($MgSO_4$), and concentrated to a volume of about 15 mL and immediately used for the following reaction described below.

2-Amino-5-(3-chloro-phenyl)-thiophene-3-carboxylic acid methyl ester

To the crude aldehyde, prepared above, in methanol was added a mixture of sulfur (2.55g, 79.44mmol), methylcyanoacetate (7.88 g, 79.44 mmol), morpholine (6.92g, 79.44) and the resulting reaction mixture was refluxed for 16 hours. The unreacted sulfur was filtered off and the filtrates were evaporated leaving behind a black residue. This residue was extracted with ether, washed with H_2O. Crystallized from ether/hexane (1:5) to obtain white crystals (3.85g, 14.3mmol, 50%), mp 85-87°; ^1H NMR (DMSO-d_6) δ 3.75 (s, 3H), 7.18-7.27 (m, 1H), 7.31-7.42 (m, 3H), 7.53 (s, 1H), 7.62 (s, 1H); MS(+APCI) m/z268(M+H); Anal. Calc. For $C_{12}H_{10}ClNO_2S$: C, 53.83, H, 3.76, N, 5.23. Found: C, 53.57, H, 3.37, N, 5.00.

2-Allyloxycarbonylamino-5-(3-chloro-phenyl)-thiophene-3-carboxylic acid methyl ester

To a solution of 2-amino-5-(3-chloro-phenyl)-thiophene-3-carboxylic acid methyl ester (2g, 7.5 mmol) in anhydrous 1,2-dichloroethane (50 mL) was added at room temperature under nitrogen allyl chloroformate (1.6 mL, 15.1 mmol). The reaction mixture was heated at reflux under nitrogen for 18 hours, cooled to room temperature, and treated with a saturated aqueous sodium bicarbonate solution (100

mL). The organic layer was separated and aqueous layer was extracted with methylene chloride (3x20 mL). The combined organic layers were washed (brine) and dried ($MgSO_4$). After removal of the solvent, the residue was purified by a flash silica gel column (hexane:ethyl acetate/7:1) to give the subtitled compound as an off-white solid (2.14g, 81%): ^{1}H-NMR (DMSO-d_6) δ 10.2 (s, 1H), 7.73 (t, 1H, J = 1.7 Hz), 7.66 (s, 1H), 7.57 (dt, 1H, J = 7.7, 1.7 Hz), 7.41 (t, 1H, J = 7.7 Hz), 7.34 (dt, 1H, J = 6.8, 1.6 Hz), 6.01 (m, 1H), 5.41 (dd, 1H, J = 7.3, 1.6 Hz), 5.29 (dd, 1H, J = 10.5, 1.3 Hz), 4.74 (d, 2H, J = 5.5 Hz), 3.84 (s, 3H). Anal. Calc. For $C_{16}H_{14}ClNO_4S$: C, 54.63, H, 4.01, N, 3.98. Found: C, 54.56, H, 3.92, N, 3.89.

To a solution of 2-allenoxycarbonylamino-5-(3-chloro-phenyl)-thiophene-3-carboxylic acid methyl ester (0.1g, 0.28 mmol) in anhydrous THF was added a solution of methylmagnesium bromide (3.0 M in diethyl ether, 1.5 mL, 4.5 mmol) at room temperature under nitrogen. After stirring at room temperature under nitrogen for 20 minutes, the reaction mixture was treated with brine (10 mL) followed by addition of an aqueous 1N HCl solution (5 mL). Ethyl acetate (20 mL) was added and organic layer was separated, washed with brine (5 mL) and dried over $MgSO_4$. After removal of solvent, the residue was purified by a flash column (silica gel, hexane:ethyl acetate/5:1) to give carbinol which was used in next step without further purification and characterization.

A mixture of above crude carbinol, potassium hydroxide (excess) in ethanol was stirred at room temperature under nitrogen overnight. The reaction solution was then acidified by an addition of a cold aqueous 1N HCl solution. Ethyl acetate (20 mL) was added and organic layer was separated, washed with brine (5 mL) and dried ($MgSO_4$). After removal of the solvent, the residue was purified by a silica gel column (hexane:ethyl acetate/2:1) to give the title compound as an off-white solid (16 mg, 19% for two steps): mp 149-150 °C; ^{1}H-NMR (DMSO-d_6) δ 10.69 (s, 1H), 7.64 (t, 1H, J = 1.8 Hz), 7.49 (s, 1H), 7.47 (dt, 1H, J = 7.7, 1.4 Hz), 7.39 (t, 1H, J = 7.8 Hz), 7.29 (dt, 1H, J = 7.8, 1.3 Hz), 1.61 (s, 6H). MS (EI) m/z 293/295 (M$^+$). Anal. Calc. For $C_{14}H_{12}ClNO_2S$: C, 57.24, H, 4.12, N, 4.77. Found: C, 57.27, H, 4.25, N, 4.66.

EXAMPLE 2

6-(3-chlrophenyl)-1,4-dihydro-4,4-dimethyl-2H-thieno[3,2-d][1,3]oxazine-2-one

3-Chloro-3-(3-chlor-phenyl)-acrylonitrile

A solution of $POCl_3$ was slowly added to anhydrous DMF over a period of 20 minutes and the temperature was maintained around 30°C. 3'-Chloroacetophenone solution in anhydrous DMF was added to the above solution and the reaction temperature was allowed to rise to around 50°C. Hydroxylamine HCl was added to the reaction solution, portionwise, over 1 hour. A volume of 500 mL of water was added to form precipitate, stirred for 1 hour and the precipitate was collected on a Büchner funnel, washed with H_2O, and dried to afford a yellow crystalline compound, mp 60-62°C. ^{1}H NMR (DMSO-d_6) δ 1.60 (s, 6H), 7.30 (d, 1H, J = 8.41Hz), 7.41 (d, 1H, J = 8.41Hz), 10.47 (s, 1H); MS(+APCI)m/z 213(M+H); Anal. Calc. For $C_9H_9ClN_2O_2$: C, 50.84, H, 4.27, N, 13.17. Found: C, 50.99, H, 4.28, N, 12.98.

3-Amino-5-(3-chloro-phenyl)-thiophene-2-carboxylic acid methyl ester

Sodium pellets were slowly added to methanol solution to form NaOMe in situ, then methyl thioglycolate was added over a period of 20 minutes to the methanol solution. A solution of 3-Chloro-3-(3-chloro-phenyl)-acrylonitrile in methanol was added slowly and was brought to reflux for 1 hour. The reaction mixture was cooled to room temperature and methanol was concentrated to 100 mL and 200 mL of water was added, stirred for 30 min and the yellow precipitate was collected and washed with water several times to yield a yellow crystalline compound, mp 92-95°C. ^{1}H NMR (DMSO-d_6) δ 1.60 (s, 6H), 7.30 (d, 1H, J = 8.41Hz), 7.41 (d, 1H, J = 8.41Hz), 10.47 (s, 1H); MS (+APCI) m/z 213(M+H); Anal. Calc. For $C_9H_9ClN_2O_2$: C, 50.84, H, 4.27, N, 13.17. Found: C, 50.99, H, 4.28, N, 12.98.

3-Allyloxycarbonylamino-5-(3-chloro-phenyl)-thiophene-2-carboxylic acid methyl ester

To a solution of 3-Amino-5-(3-chloro-phenyl)-thiophene-2-carboxylic acid methyl ester (15g, 56.0mmol) in toluene (200mL) was added a solution of allyl chloroformate (8.10g, 67.2mmol) in toluene (5.0mL) and the resulting reaction solution was heated under reflux for 3 hours. Toluene was stripped down and the crystals were collected and washed with ether/hexane to afford a yellow crystalline compound, mp 101-103°C. ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3H), 4.68-4.71 (d, 2H, J = 5.46Hz), 5.26-5.30 (dd, 1H, J = 1.35, 9.84Hz), 5.36-5.42 (dd, 1H, J = 1.57, 15.68Hz), 5.96 (m, 2H), 7.50-7.52 (m, 2H), 7.67-7.71 (m, 1H), 7.79 (s, 1H), 8.10 (s, 1H); MS(+APCI) m/z 352(M+H); Anal. Calc. For $C_{16}H_{14}ClNO_4S$: C, 54.63, H, 4.01, N, 3.97. Found: C, 54.05, H, 4.17, N, 3.84.

[5-(3-Chloro-phenyl)-2-(1-hydroxy-1-methyl-ethyl)-thiophen-3-yl]-carbamic acid allyl ester

To a solution of 3-Allyloxycarbonylamino-5-(3-chloro-phenyl)-thiophene-2-carboxylic acid methyl ester (5.3g, 15.1mmol) in anhydrous THF (30mL) at room temperature was added a solution of 3.0M MeMgI in ether (20.1mL, 60.24mmol). After 30 minutes, the reaction was slowly quenched with H_2O (10mL), treated with saturated NH_4OH (100mL), extracted with ether (200mL), washed with brine, dried ($MgSO_4$), concentrated, and chromatographed (hexane/ether, 1:4): mp 60-61; ^{1}H NMR (DMSO-d_6) δ 1.52 (s, 6H), 4.59-4.61 (d, 2H, J = 5.35Hz), 5.22-5.36 (m, 2H), 5.91-6.04 (m, 2H), 7.33-7.67 (m, 5H), 8.89 (s, 1H); MS(EI) m/z 351/353(M+H); Anal. Calc. For $C_{17}H_{18}ClNO_3S$: C, 58.03, H, 5.16, N, 3.98. Found: C, 58.17, H, 5.16, N, 3.97.

6-(3-Chlorophenyl)-1,4-dihyrdro-4,4-dimethyl-2H-thieno[3,2-d][1,3]oxazin-2-one

To a solution of [5-(3-Chloro-phenyl)-2-(1-hydroxy-1-methyl-ethyl)-thiophen-3-yl]-carbamic acid allyl ester (.12g, .34mmol) in anhydrous THF (5.0mL) was added

KO^{t}Bu (0.076g, 0.068mmol) and stirred for 15 min, quenched with H_2O, and in situ crystallization was carried out by adding minimal amount of MeOH to the solution. The white crystals were collected on a Büchner funnel, mp 123-125°C. ^{1}H NMR (DMSO-d_6) δ 1.64 (s, 6H), 7.05 (s, 1H), 7.37-7.48 (m, 2H), 7.53-7.56 (s, 1H), 7.67-7.68 (m, 1H), 10.41 (s, 1H); MS(EI) m/z 293/295(M+H); Anal. Calc. For $C_{17}H_{18}ClNO_3S$: C, 57.24, H, 4.12, N, 4.77. Found: C, 56.93, H, 3.92, N, 4.97.

Example 3 - Pharmacology

The progestational activity of the current invention was evaluated in the PRE-luciferase assay in CV-1 cells, described below. *In-vitro* potencies can be in the range 0.01nM-10,000nM. *In vivo* potencies are anticipated to be in the range 1 mg/kg to 30 mg/kg.

The object of this assay is to determine a compound's progestational or antiprogestational potency based on its effect on PRE-luciferase reporter activity in CV-1 cells co-transfected with human PR and PRE-luciferase plasmids. The materials methods used in the assay are as follows.

a. Medium: The growth medium was as follows: DMEM (BioWhittaker) containing 10% (v/v) fetal bovine serum (heat inactivated), 0.1 mM MEM non-essential amino acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL). The experimental medium was as follows: DMEM (BioWhittaker), phenol red-free, containing 10% (v/v) charcoal-stripped fetal bovine serum (heat-inactivated), 0.1 mM MEM non-essential amino acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

b. Cell culture, transfection, treatment, and luciferase assay

Stock CV-1 cells are maintained in growth medium. Co-transfection is done using $1.2x10^7$ cells, 5 mg pLEM plasmid with hPR-B inserted at SphI and BamHI sites, 10 mg pGL3 plasmid with two PREs upstream of the luciferase sequence, and 50 mg sonicated calf thymus DNA as carrier DNA in 250 ml.

Electroporation is carried out at 260 V and 1,000 mF in a Biorad Gene Pulser II. After electroporation, cells are resuspended in growth medium and plated in 96-well plate at 40,000 cells/well in 200 µl. Following overnight incubation, the medium is changed to experimental medium. Cells are then treated with reference or test compounds in experimental medium. Compounds are tested for antiprogestational activity in the presence of 3 nM progesterone. Twenty-four hr. after treatment, the medium is discarded, cells are washed three times with D-PBS (GIBCO, BRL). Fifty µl of cell lysis buffer (Promega, Madison, WI) is added to each well and the plates are shaken for 15 min in a Titer Plate Shaker (Lab Line Instrument, Inc.). Luciferase activity is measured using luciferase reagents from Promega.

c. Analysis of Results:

Each treatment consists of at least 4 replicates. Log transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is used to downweight the effects of outliers. EC_{50} or IC_{50} values are calculated from the retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way analysis of variance and non-linear response analyses.

d. Reference Compounds:

Progesterone and trimegestone are reference progestins and RU486 is the reference antiprogestin. All reference compounds are run in full dose-response curves and the EC_{50} or IC_{50} values are calculated.

Table 1. Estimated EC_{50}, standard error (SE), and 95% confidence intervals (CI) for reference progestins from three individual studies

		EC50		95% CI	
Compound	Exp.	(nM)	SE	lower	upper
Progesterone	1	0.616	0.026	0.509	0.746
	2	0.402	0.019	0.323	0.501
	3	0.486	0.028	0.371	0.637
Trimegestone	1	0.0075	0.0002	0.0066	0.0085
	2	0.0081	0.0003	0.0070	0.0094
	3	0.0067	0.0003	0.0055	0.0082

Table 2. Estimated IC_{50}, standard error (SE), and 95% confident interval (CI) for the antiprogestin, RU486 from three individual studies

		IC 50		95% CI	
Compound	Exp.	(nM)	SE	lower	upper
RU486	1	0.028	0.002	0.019	0.042
	2	0.037	0.002	0.029	0.048
	3	0.019	0.001	0.013	0.027

Progestational activity: Compounds that increase PRE-luciferase activity significantly ($p<0.05$) compared to vehicle control are considered active.

Antiprogestational activity: Compounds that decrease 3 nM progesterone induced PRE-luciferase activity significantly ($p<0.05$)

EC_{50}: Concentration of a compound that gives half-maximal increase PRE-luciferase activity (default-nM) with SE.

IC_{50}: Concentration of a compound that gives half-maximal decrease in 3 nM progesterone induced PRE-luciferase activity (default-nM) with SE.

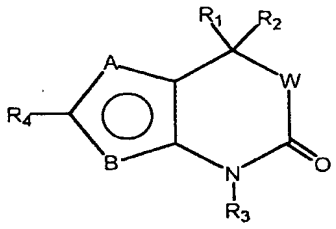
All publications cited in this specification are incorporated herein by reference herein. While the invention has been described with reference to a particularly preferred embodiment, it will be appreciated that modifications can be made without departing from the spirit of the invention. Such modifications are intended to fall within the scope of the appended claims.

What is Claimed:

1. A method of contraception which comprises administering to a female of child bearing age for 28 consecutive days:

a) a first phase of from 14 to 24 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 100 µg levonorgestrel;

b) a second phase of from 1 to 11 daily dosage units, at a daily dosage of from about 2 to 50 mg, of an antiprogestin compound of Formula I:



I

wherein:

A and B are independent substituents selected from S, CH or N;

Provided that when A is S, B is CH or N; provided that

when B is S, A is CH or N;

and A and B cannot both be CH;

and when A and B both equal N, one N may be optionally substituted with an C_1 to C_6 alkyl group;

R_1 and R_2 are independent substituents selected from the group of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

or R^1 and R^2 are fused to form:

a) an optionally substituted 3 to 8 membered spirocyclic alkyl ring; or

b) an optionally substituted 3 to 8 membered spirocyclic alkenyl ring; or

c) an optionally substituted 3 to 8 membered spirocyclic ring containing one to three heteroatoms selected from the group of O, S and N;

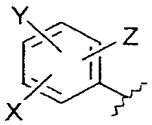
R^A is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^B is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^3 is H, OH, NH_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_1 to C_6 alkenyl, alkynyl, or substituted alkynyl, or COR^C;

R^C is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^4 is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below,



X is selected from halogen, CN, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 thioalkyl, substituted C_1 to C_3 thioalkyl, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2, C_1 to C_3 perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D, $OCOR^D$, or NR^ECOR^D;

R^D is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^E is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

Y and Z are independently selected from H, halogen, CN, NO_2, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, or C_1 to C_3 thioalkyl;

or

R^4 is a five or six membered ring with 1, 2, or 3 heteroatoms selected from O, S, SO, SO_2 or NR^5, the five or six membered rings being optionally substituted by one or two independent substituents selected from H, halogen, CN, NO_2 and C_1 to C_3 alkyl, C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, COR^F, or NR^GCOR^F;

R^F is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^G is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^5 is H, or C_1 to C_3 alkyl;

W is O or a chemical bond;

or a pharmaceutically acceptable salt thereof; and

c) optionally, a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo for the remaining days of the 28 consecutive days

in which no antiprogestin, progestin or estrogen is administered; wherein the total daily dosage units of the first, second and third phases equals 28.

2. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound is selected from those of Formula 1 of Claim 1 wherein:

A and B are independent substituents S, CH or N,

provided that when A is S, B is CH or N; and

when B is S, A is CH or N; and

A and B cannot both be CH; and

when A and B both equal N, one N may be optionally substituted with an C_1 to C_6 alkyl group;

R^1 is H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

R^2 is H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

or R^1 and R^2 are fused to form:

a) an optionally substituted 3 to 8 membered spirocyclic alkyl ring; or

b) an optionally substituted 3 to 8 membered spirocyclic alkenyl ring; or

c) an optionally substituted 3 to 8 membered spirocyclic ring containing one to three heteroatoms selected from the group of O, S and N;

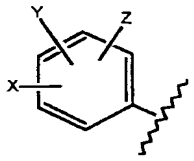
R^A is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^B is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^3 is H, OH, NH_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_1 to C_6 alkenyl, alkynyl, or substituted alkynyl, or COR^C;

R^C is H, C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, aryl, substituted aryl, C_1 to C_4 alkoxy, substituted C_1 to C_4 alkoxy, C_1 to C_4 aminoalkyl, or substituted C_1 to C_4 aminoalkyl;

R^4 is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below:



X is taken from the group including halogen, CN, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 thioalkyl, substituted C_1 to C_3 thioalkyl, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2, C_1 to C_3 perfluoroalkyl, 5-membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D, $OCOR^D$, or NR^ECOR^D;

R^D is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^E is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

Y and Z are independent substituents taken from the group including H, halogen, CN, NO_2, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, or C_1 to C_3 thioalkyl;

or

R^4 is a five or six membered ring with 1, 2, or 3 heteroatoms selected from O, S, SO, SO_2 or NR^5 , the five or six membered ring being optionally substituted by one or two independent substituents selected from H, halogen, CN, NO_2 and C_1 to C_3 alkyl, or C_1 to C_3 alkoxy;

R^5 is H or C_1 to C_3 alkyl;

W is O or a chemical bond

or a pharmaceutically acceptable salt thereof.

3. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound is selected from those of Formula 1 of Claim 1 wherein:

A and B are independent substituents from the group including S, CH or N;

provided that when A is S, B is CH or N; and

when B is S, A is CH or N; and

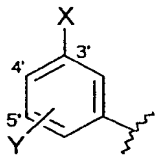
A and B cannot both be CH;

R^1 = R^2 and are selected from the group which includes C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, or spirocyclic alkyl constructed by fusing R^1 and R^2 to form a 3 to 6 membered spirocyclic ring;

R^3 is H, OH, NH_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, or COR^C;

R^C is H, C_1 to C_4 alkyl, or C_1 to C_4 alkoxy;

R^4 is a disubstituted benzene ring containing the substituents X and Y as shown below:

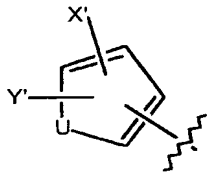


X is selected from the group including halogen, CN, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, NO_2, C_1 to C_3 perfluoroalkyl, 5 membered heterocyclic ring containing 1 to 3 heteroatoms, or C_1 to C_3 thioalkyl;

Y is a substituent on the 4' or 5' position selected from the group of H, halogen, CN, NO_2, C_1 to C_3 alkoxy, C_1 to C_4 alkyl, or C_1 to C_3 thioalkyl;

or

R^4 is a five membered ring with the structure shown below:



U is O, S, or NR^5;

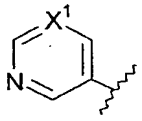
R^5 is H, or C_1 to C_3 alkyl, or C_1 to C_4 CO_2alkyl;

X' is selected from halogen, CN, NO_2, C_1 to C_3 alkyl or C_1 to C_3 alkoxy;

Y' is H or C_1 to C_4 alkyl;

or

R^4 is a six membered ring with the structure:



X^1 is N or CX^2,

X^2 is halogen, CN or NO_2;

W is O or a chemical bond;

or a pharmaceutically acceptable salt thereof.

4. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound is selected from those of Formula 1 of Claim 1 wherein:

$R^1 = R^2$ and are selected from the group which includes C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, or spirocyclic alkyl constructed by fusing R^1 and R^2 to form a 3 to 6 membered spirocyclic ring;

and A, B, R^3, R^C, R^4, X, Y, U, R^5, X', Y', X^1, X^2, R^6, R^7, R^8, R^9 and W are as defined in Claim 3;

or a pharmaceutically acceptable salt thereof.

5. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound is selected from those of Formula 1 of Claim 1 wherein:

R^1 and R^2 are fused to form a 3 to 6 membered spirocyclic ring;

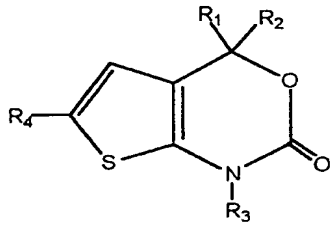
and A, B, R^3, R^C, R^4, X, Y, U, R^5, X', Y', X^1, X^2, R^6, R^7, R^8, R^9 and W are as defined in Claim 3;

or a pharmaceutically acceptable salt thereof.

6. A method of contraception which comprises administering to a female of child bearing age for 28 consecutive days:

a) a first phase of from 14 to 24 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 100 μg levonorgestrel;

b) a second phase of from 1 to 11 daily dosage units, at a daily dosage of from about 2 to 50 mg, of an antiprogestin compound of the formula:



wherein:

R_1 and R_2 are independent substituents selected from the group of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

or R^1 and R^2 are fused to form:

a) a 3 to 6 membered spirocyclic alkyl ring; or

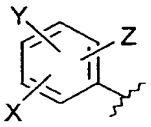
b) a 3 to 6 membered spirocyclic alkenyl ring;

R^3 is H, OH, NH_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_1 to C_6 alkenyl, alkynyl, or substituted alkynyl, or COR^C;

R^B is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^C is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^4 is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below,



X is selected from halogen, CN, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 thioalkyl, substituted C_1 to C_3 thioalkyl, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2, C_1 to C_3 perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D, $OCOR^D$, or NR^ECOR^D;

R^D is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^E is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl; and

Y and Z are independently selected from H, halogen, CN, NO_2, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, or C_1 to C_3 thioalkyl; or a pharmaceutically acceptable salt thereof; and

c) optionally, a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo for the remaining days of the 28 consecutive days in which no antiprogestin, progestin or estrogen is administered; wherein the total daily dosage units of the first, second and third phases equals 28.

7. A method of Claim 1 in which the antiprogestin compound is 6-(3-chlorophenyl)-1,4-dihydro-4,4-dimethyl-2H-thieno[2,3-d][1,3]oxazine-2-one, or a pharmaceutically acceptable salt thereof.

8. The method of Claim 1 wherein the progestational agent is selected from the group of levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethindrone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, drospirenone, nomegestrol, or (17-deacetyl)norgestimate.

9. A method of Claim 1 which comprises administering to a female of child bearing age consecutively over a 28 day cycle:

a) a first phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 100 μg levonorgestrel;

b) a second phase of 3 daily dosage units of an antiprogestin compound of Claim 1, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and

c) optionally, 4 daily dosage units of an orally and pharmaceutically acceptable placebo to be administered on each day of the 28-day cycle following the first phase and second phase.

10. A method of contraception which comprises administering to a female of child bearing age over a period of 28 consecutive days:

a) a first phase of from 18 to 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel, and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg; and

b) a second phase of from 1 to 7 daily dosage units of an antiprogestin of Claim 1 at a daily dose of from about 2 to 50 mg; and

c) optionally, an orally and pharmaceutically acceptable placebo for each remaining day of the 28 consecutive days.

11. A method of contraception of Claim 10 which comprises administering to a female of child bearing age over a period of 28 consecutive days:

a) a first phase of 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 100 μg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg; and

b) a second phase of 3 daily dosage units of an antiprogestin of Claim 1 at a daily dose of from about 2 to 50 mg; and

c) optionally, a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

12. A method of contraception which comprises administering to a female of child bearing age over a period of 28 consecutive days:

a) a first phase of from 18 to 21 daily dosage units containing a progestational agent at a daily dose equal in progestational activity to from about 35 to about 150 μg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg

b) a second phase of from 1 to 7 daily dose units, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg and ethinyl estradiol at a concentration of from about 10 to about 35 μg; and

c) optionally, a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo, the total of the daily dosage units being 28.

13. A method of contraception of Claim 12 which comprises administering to a female of child bearing age over a period of 28 consecutive days:

a) a first phase of 21 daily dosage units, each daily dosage unit containing a progestational agent at a daily dose equal in progestational activity to about 35 to about 100 μg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg

b) a second phase of 3 daily dose, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 μg; and

c) optionally, a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

14. A pharmaceutically useful kit adapted for daily oral administration which comprises:

a) a first phase of from 14 to 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel;

b) a second phase of from 1 to 11 daily dosage units of an antiprogestin compound of Claim 1, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and

c) a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo;

wherein the total number of the daily dosage units in the first phase, second phase and third phase equals 28.

15. A pharmaceutically useful kit adapted for daily oral administration of Claim 14 which comprises:

a) a first phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel;

b) a second phase of 3 daily dosage units of an antiprogestin compound of Claim 1, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and

c) a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

16. A pharmaceutically useful kit adapted for daily oral administration which comprises:

a) a first phase of from 18 to 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg; and

b) a second phase of from 1 to 7 daily dosage units of an antiprogestin of Claim 1 at a daily dose of from about 2 to 50 mg; and

c) a third phase of from 0 to 9 daily dosage units of an orally and pharmaceutically acceptable placebo;

wherein the total number of the daily dosage units in the first phase, second phase and third phase equals 28.

17. A pharmaceutically useful kit adapted for daily oral administration of Claim 16 which comprises:

a) a first phase of 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg; and

b) a second phase of three daily dosage units of an antiprogestin of Claim 1 administered at a daily dose of from about 2 to 50 mg; and

c) a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

18. A pharmaceutically useful kit adapted for daily oral administration which comprises:

a) a first phase of from 18 to 21 daily dosage units, each daily dosage unit comprising a progestational agent at a daily dose equal in progestational activity to from about 35 to about 150 μg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg

b) a second phase of from 1 to 7 daily dose units, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 μg; and

c) a third phase of from 0 to 9 daily dosage units of an orally and pharmaceutically acceptable placebo;

wherein the total number of the daily dosage units in the first phase, second phase and third phase equals 28.

19. A pharmaceutically useful kit adapted for daily oral administration of Claim 18 which comprises:

a) a first phase of 21 daily dosage units, each containing a progestational agent of this invention at a daily dose equal in progestational activity to about 35 to about 150 μg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg

b) a second phase of 3 daily dose units, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 μg; and

c) a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

INTERNATIONAL SEARCH REPORT

Intex onal Application No
PCT/US 00/11846

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P15/18 A61K45/06 A61K31/57 A61K31/565 //(A61K31/57, 31:54,31:565),(A61K31/57,31:535,31:565)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, MEDLINE, SCISEARCH, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 696 133 A (HAMANN LAWRENCE G ET AL) 9 December 1997 (1997-12-09) claims 1,4,5 ---	1-19
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Y	DE 43 30 234 A (SCHERING AG) 9 March 1995 (1995-03-09) column 1, line 1 - line 30 claims 1-8 ---	1-19
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 August 2000	19/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bonzano, C

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 00/11846

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 15794 A (BALANCE PHARMACEUTICALS INC) 30 May 1996 (1996-05-30) page 6, line 15 -page 7, line 23 ---	1-19
Y	WO 97 49407 A (AKZO NOBEL NV ;COELINGH BENNINK HERMAN JAN TI (NL); VERBOST PIETER) 31 December 1997 (1997-12-31) page 2, line 29 -page 3, line 6 ---	1-19
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-6,8-19 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Present claims 1,6-7,9-19 relate to a compound defined by reference to a desirable characteristic or property, namely the progestational activity. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the combinations containing the compounds explicitely mentioned in the examples of the description, with due regard to the general idea underlying the present invention.

Claims searched completely: none.
Claims searched incompletely: 1-19.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

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Inter onal Application No
PCT/US 00/11846

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(30) Priority Data:

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(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:

US	Not furnished (CON)
Filed on	19 April 2000 (19.04.2000)

(71) Applicants *(for all designated States except US)*: **AMERICAN HOME PRODUCTS CORPORATION** [US/US]; Five Giralda Farms, Madison, NJ 07840 (US). **LIGAND PHARMACEUTICALS, INC.** [US/US]; 10275 Science Center Drive, San Diego, CA 92121 (US).

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(75) Inventors/Applicants *(for US only)*: **GRUBB, Gary, S.** [US/US]; 825 Briarwood Road, Newtown Square, PA 19073 (US). **ZHI, Lin** [CN/US]; 7794 Roan Road, San Diego, CA 92129 (US). **JONES, Todd, K.** [US/US]; 546 Marview Drive, Solana Beach, CA 92075 (US). **SANTILLI, Arthur, A.** [US/US]; 1737 Sue Ellen Drive, Havertown, PA 19083 (US). **TEGLEY, Christopher, M.** [US/US]; 478 Thunderhead Street, Thousand Oaks, CA 91360 (US). **VIET, Andrew, Q.** [US/US]; Apt. L-200, 250 Beverly Boulevard, Upper Darby, PA 19082 (US). **ZHANG, Puwen** [CN/US]; 7004 Oriole Court, Audubon, PA 19403 (US). **FENSOME, Andrew** [GB/US]; 779 Trephanny Lane, Wayne, PA 19087 (US). **WROBEL, Jay, E.** [US/US]; 15 Rosetree Lane, Lawrenceville, NJ 08648 (US). **EDWARDS, James, P.** [US/US]; 8723 Hesby Court, San Diego, CA 92129 (US).

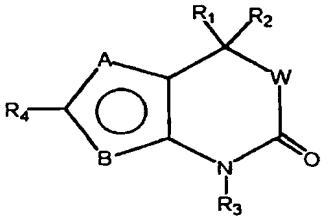
(74) Agents: **KODROFF, Cathy, A.** et al.; Howson and Howson, Spring House Corporate Center, P.O. Box 457, Spring House, PA 19477 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent

[Continued on next page]

(54) Title: CONTRACEPTIVE COMPOSITIONS CONTAINING CYCLIC CARBAMATES AND AMIDE DERIVATIVES



(I)

(57) Abstract: This invention relates to cyclic combination therapies and regimens utilizing, in combination with progestins, estrogens, or both, substituted indoline derivative compounds which are antagonists of the progesterone receptor having general structure (I) wherein A and B are independent substituents selected from S, CH or N; provided that when A is S, B is CH or N; and when B is S, A is CH or N; and A and B cannot both be CH; and when A and B both equal N, one N may be optionally substituted with a C_1 to C_6 alkyl group; R_1 and R_2 are independent substituents selected from the group of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A; or R^1 and R^2 are fused to form optionally substituted 3 to 8 membered spirocyclic alkyl, alkenyl or heterocyclic ring, the heterocyclic ring containing one to three heteroatoms selected from the group of O, S and N; or pharmaceutically useful salts thereof. These methods of treatment may be used for contraception or for the treatment and/or prevention of secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis; polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, or minimization of side effects or cyclic menstrual bleeding. Additional uses of the invention include stimulation of food intake.

WO 00/66225 A1

(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.